Core Safeguards for Clinical Research with Adults Who Are Unable To Consent

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The National Bioethics Advisory Commission has proposed new safeguards for clinical research with adults who are unable to consent. Three other major U.S. groups have also proposed additional safeguards for this population, and existing Canadian and European guidelines already include such safeguards. While these six guidelines agree on some safeguards, they disagree on others. To allow important research to proceed while protecting adults who are unable to consent, it will be crucial to resolve these differences. This paper uses a side-by-side comparison of these six guidelines to highlight their major points of consensus, analyze their significant differences, and distill six core safeguards.

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Historically, the reputation of clinical research has been tarnished and its progress thwarted by the performance of studies on human subjects without their informed consent. Familiar examples include the Tuskegee syphilis study and the experiments performed on prisoners in Nazi concentration camps. More recently, there has been renewed concern that abuses may again undermine clinical research, this time as the result of research on patients who are *unable* to give informed consent. This concern has been fueled by two incidents.

In 1991, three legal advocacy groups sued on behalf of six psychiatric patients hospitalized in New York State who feared that existing regulations might permit investigators to enroll them in clinical research inappropriately. The resulting decision in *T.D. v. New York State Office of Mental Health* threatened to shut down a good deal of important research (1). An investigation by the U.S. Office of Protection from Research Risks into the suicide of a schizophrenic patient who had recently participated in a research trial at the University of California, Los Angeles (UCLA), raised questions about the extent to which patients who are unable to consent, and those who are at risk for losing the ability to consent, are adequately protected (2). Regardless of whether these cases involved actual abuses, they have highlighted a major failing of the current regulatory reliance on informed consent: It does not sufficiently protect persons who are unable to consent.

The U.S. Code of Federal Regulations does not include specific protections for persons who are unable to consent beyond the possibility of obtaining the permission of the impaired persons' surrogates (3). The UCLA investigation and *T.D. v. New York State Office of Mental Health* raise concerns about the lack of adequate protections at the state level. Finally, a recent study found that this gap exists at the institutional level as well; 80% of research institutions designated as "Alzheimer's Disease Centers" by the National Institute on Aging do not have their own policies for research with cognitively impaired patients (4).

In response to these concerns, four major U.S. groups have proposed additional safeguards for adults who are unable to consent (5–8). Two international guidelines already include such safeguards (9, 10). We use a side-by-side comparison of these six policies to highlight their major points of consensus, analyze their significant differences, and distill six core safeguards for clinical research with adults who are unable to consent.

The Six Groups

The National Bioethics Advisory Commission (NBAC), charged with providing advice to the President on the protection of human research subjects, has proposed additional safeguards for "research involving persons with mental disorders that may affect decision making capacity" (5). Several branches of the National Institutes of Health (NIH) developed Points to Consider for research on "individuals who are, may be, or may become decisionally impaired" (8). At the state level, the Maryland Attorney General's office developed regulations for "decisionally incapacitated subjects" (7) and, in response to *T.D. v. New York State Office of Mental Health*, a New York Department of Health advisory group endorsed guidelines on "research involving those unable to consent" (6). Internationally, the Cana-

Table 1. **Scope of the Recommendations***

Variable	NIH	NBAC	Maryland	New York	Canadian Tri-Council	Council of Europe	Current Proposal
Population covered	Impaired and at-risk adults	Adults with mental disorders	Incapacitated and at-risk adults	Incapacitated adults	Incompetent adults	Adults unable to consent	Adults unable to consent to nonemergency research
Apply to children?	No	No	No	No	Yes	Yes	No
When applied	Enrollment–continued participation	Enrollment	Enrollment–continued participation	Enrollment–continued participation	Enrollment–continued participation	Not mentioned	Enrollment–continued participation

* NBAC = National Bioethics Advisory Commission; NIH = National Institutes of Health.

dian Tri-Council regulations represent a consensus of the Medical Research, Natural Sciences and Engineering, and Social Sciences and Humanities Councils (9); the Council of Europe's recommendations have been signed by 24 members (10). Although the Canadian and European policies cover all clinical research, they include safeguards for patients who are unable to consent.

WHICH GROUPS OF PATIENTS SHOULD BE COVERED?

The Council of Europe and the Canadian Tri-Council guidelines cover adults and children in both emergency and nonemergency situations (**Table 1**). The four U.S. groups limit their proposals to adults in nonemergency situations. The NBAC's safeguards cover adults with "mental disorders," and the Maryland, New York, and NIH proposals apply to adults who are "cognitively" or "decisionally" impaired.

Because of several crucial differences, research with adults who are unable to consent in nonemergency situations deserves its own policy. For example, one of the central safeguards for adults who cannot consent—evidence of their wishes when they were competent—does not apply to children, while the consent of a proxy frequently cannot be obtained in emergency settings.

Although the four U.S. guidelines support a separate policy for adults who are unable to consent in nonemergency settings, their focus on specific subgroups may cause confusion and leave some persons unprotected. For instance, the NBAC's focus on persons with "mental disorders" seems vague and does not protect adults who are unable to consent because of other conditions, such as stroke and brain tumors. Similarly, it may be unclear whether a widower, unable to consent because of depression, is "cognitively" or "decisionally" impaired. As a result, he may not be protected under the Maryland, New York, and NIH proposals.

The scopes of these policies are determined by the reasons why persons are unable to consent, such as mental disorders, cognitive impairment, or decisional impairment. However, the need for additional safeguards does not depend on *why* adults are unable to consent, only *that* they are unable to consent. This suggests that one way to eliminate any confusion about who is covered would be to apply the additional safeguards to all adults who cannot consent, regardless of the reasons.

The Maryland, New York, NBAC, NIH, and Canadian Tri-Council guidelines also cover adults who are at risk for losing the ability to consent, such as those with schizophrenia entering a drug washout trial. Specifically, these persons are encouraged to designate a proxy decision maker and to indicate their research preferences ahead of time.

THE CORE SAFEGUARDS

The six guidelines endorse six core safeguards that we consider in order, from the initial review of a research protocol through its execution: 1) institutional risk–benefit assessment, 2) consent assessment, 3) necessity requirement, 4) proxy decision maker and sufficient evidence of patients' remaining preferences and interests, 5) respect for patient assent and dissent, and 6) independent monitors (**Table 2**).

Institutional Review Board Risk–Benefit Assessment

The six guidelines require institutional review boards to assign a risk level to all protocols that propose to include adults who are unable to consent. Following the U.S. regulations for children (3), the New York and Maryland guidelines use three risk levels: 1) minimal risk, 2) minor increment over minimal risk, and 3) greater than a minor increment over minimal risk. In

Table 2. **Core Safeguards***

Variable	NIH	NBAC	Maryland	New York	Canadian Tri-Council	Council of Europe	Current Proposal
IRB risk–benefit assessment	Sliding scale–benefit undefined	Two risk levels–"may" benefit	Three risk levels–"realistic possibility"	Three risk levels–"realistic possibility"	Two risk levels–benefit undefined	Two risk levels–benefit undefined	Three risk levels–"clinically equivalent" research
Consent assessment	Assess participants with potentially incapacitating conditions	Assess participants with mental disorders	Assess patients with potentially incapacitating conditions	Assess patients with potentially incapacitating conditions	Assume competency	Not mentioned	Assess all participants
Necessity requirement	Not mentioned	Yes	Yes	Yes, "ordinarily"	Yes	Yes	Yes
Participant's condition requirement	Not mentioned	Yes	Yes	When plan to enroll	No	No	No
Proxy decision maker and sufficient evidence of patients' preferences and interests							
Proxy required	May have proxy	Yes	Yes	Yes	Yes	Yes	Yes
Evidence of participant's preferences	Advance directive may be used	Advance directive required for riskier research	Advance directive required for riskier research	Advance directive required for riskier research	Advance directive required for riskier research	Not mentioned	More evidence required for riskier research
Assent–dissent	Assent necessary–dissent sufficient	Dissent sufficient	Assent necessary–dissent sufficient	Assent necessary–dissent sufficient unless court order	Assent necessary–dissent sufficient unless potential benefit	Dissent sufficient	Assent necessary–dissent sufficient
Independent monitors							
Consent monitors	Considered	Considered	Required for research with greater than a minor increment over minimal risk and no potential benefit	Required for research with greater than a minor increment over minimal risk and no potential benefit	Considered as risks increase	Not mentioned	Required for research that is not clinically equivalent and involves greater than a minor increment over minimal risk
Participation monitors	Considered	No	For research with greater than a minimal risk and no potential benefit	For research with greater than a minor increment over minimal risk and no potential benefit	Considered	Not mentioned	Required for research with greater than a minor increment over minimal risk

* IRB = institutional review board; NBAC = National Bioethics Advisory Commission; NIH = National Institutes of Health.

contrast, the NBAC, the Canadian Tri-Council, and the Council of Europe guidelines use two risk levels—minimal risk and greater than minimal risk—while the NIH guidelines do not use discrete risk levels but instead endorse a sliding risk scale.

As the NIH proposal recognizes, research risks are continuous. Nonetheless, most of the proposed safeguards apply or not in a particular case. For instance, persons can have a proxy decision maker or not. To allow institutional review boards to match discrete safeguards to particular protocols, a final policy that divides risks into distinct levels may be easier to implement.

There is no a priori reason to prefer one number of risk levels to another. Rather, the number of risk levels incorporated into a final policy should be based on the number of different combinations of safeguards that are

needed to provide appropriate protection. Therefore, to determine the appropriate number of distinct risk levels, it is first necessary to fix the required number of safeguard combinations.

The six guidelines agree that institutional review boards should mandate fewer safeguards for research that offers participants the potential for direct benefit. Although this makes sense, it seems that the number of safeguards should be reduced only when the potential for benefit outweighs the risks participants face. The NBAC guidelines, which refer to research that "may" benefit participants, as well as the Maryland and New York guidelines, which refer to a "realistic possibility" of helping participants, do not seem to capture this distinction. One possibility would be to follow the U.S. Code of Regulations on research with children and stipulate that protocols qualify as having the "potential" for direct benefit only if, in the judgment of the institutional review board, 1) the protocol's potential for direct benefit justifies its risks and 2) the protocol's risk–benefit profile is at least as favorable as the available alternatives (3).

The Council of Europe guidelines prohibit research that does not offer the potential for direct benefit and poses greater than minimal risks. The other five guidelines agree that persons who are unable to consent can be adequately protected without placing a risk ceiling on research that does not offer the potential for direct benefit.

Consent Assessment

The Canadian Tri-Council guidelines consider persons to be competent to consent barring evidence to the contrary. Apart from the Council of Europe, the other guidelines advocate assessment of the competence of targeted groups. The NBAC would assess persons with mental disorders who are being considered for more than minimal-risk research, Maryland would assess persons with potentially incapacitating conditions, and New York and the NIH would assess those who are and those who are likely to become incapacitated.

These attempts to determine precisely which types of patients should be assessed have led to a seemingly endless debate. Are persons with a personal history of stroke sufficiently at risk to justify a competence assessment? What about persons older than 50 years of age who have a family history of Alzheimer disease? Although there does not seem to be any way to answer these questions definitively, the widespread recommendation that investigators assess the understanding of all potential research participants offers a way to avoid this difficulty altogether.

Investigators could briefly assess the understanding of all participants, for instance, by asking them to briefly re-explain the protocol in their own words. When participants are unable to do this, investigators could attempt to enhance their understanding (11). Overly anxious persons could be given an anxiolytic; persons with metabolic encephalopathy due to temporary kidney failure could be treated and approached later. When attempts to enhance participants' understanding fail, the investigator could give a more formal assessment and then implement the appropriate safeguards for those who are determined to be unable to consent. This approach underscores the importance of assessing the informed consent of all research participants. It also avoids stigmatizing persons who are targeted for assessment under more selective policies and avoids missing those who are unable to consent but are not targeted by these policies.

Necessity Requirement

With the exception of the NIH, the guidelines agree that adults who are unable to consent should be enrolled only when investigators cannot obtain the desired information by enrolling adults who can consent. There is disagreement, however, over whether this "necessity" requirement should be applied to protocols that offer the potential for direct benefit. Should persons with severe Alzheimer disease be barred from protocols that offer a chance to cure metastatic cancer because the investigators could just as easily enroll persons who can consent? The Council of Europe and Canadian Tri-Council guidelines would bar these persons; the New York guidelines would not.

Such exclusions might seem discriminatory and misguided, denying patients access to important treatments in the name of protecting them. However, enrolling persons who are unable to consent when enough willing persons can consent increases a protocol's potential for exploitation. To minimize this potential, it seems better to exclude persons who cannot consent when their participation is unnecessary. In cases where these

persons are thereby denied access to experimental treatments that may be in their best interests, further assessment could determine whether they should be offered these treatments outside of the research context (for instance, in "expanded access" programs). This approach would avoid conflating the scientific needs of research with the medical needs of persons who are unable to consent and would avoid even the appearance of exploitation.

None of the proposals address the risks associated with "add-on" procedures (12). For instance, investigators often obtain biological samples from research participants for non–protocol-related purposes. To ensure that such procedures do not unnecessarily expose persons who are unable to consent to serious risks, a consensus policy might adopt a broad necessity requirement stipulating that persons who are unable to consent should be necessary for the protocol as a whole and for any purely research procedures that pose more than minimal risk.

The New York, Maryland, and NBAC guidelines would reinforce the necessity requirement with the so-called "subject's condition" requirement, which states that persons who are unable to consent may be enrolled only when the research concerns the condition responsible for their incapacity. However, as the expert panel consulted by the NIH points out, the enrollment of persons who cannot consent may sometimes be necessary for research on diseases they do not have (13). For instance, comparing the brain scans of persons who are unable to consent because of one mental disorder can be crucial to understanding the cause of a second mental disorder.

Sufficient Evidence and Proxy Decision Makers

Adults who lose the ability to make their own research decisions nonetheless retain at least some preferences and interests (14, 15). Persons who are rendered unconscious by head trauma or stroke typically retain the preferences and interests they had just before the injury; even persons with severe Alzheimer disease retain some preferences and interests. Consequently, the six guidelines agree that adults who have lost the ability to consent should participate in research only when it is consistent with their remaining preferences and interests.

Of course, adults who have lost the ability to consent often cannot communicate their remaining preferences and interests. Thus, in deciding whether to enroll these persons, investigators must appeal to any evidence of their competent preferences and interests. Barring reason to believe otherwise, persons are assumed to retain their competent preferences and interests.

There is consensus that enrollment in research with the potential for direct benefit does not require positive evidence of persons' remaining preferences and interests. In this case, research enrollment is acceptable provided there is no evidence that enrollment is inconsistent with the person's remaining preferences and interests. The guidelines further agree that enrollment in research that does not offer the potential for direct benefit requires positive evidence of the person's remaining preferences and interests. More evidence is needed as the risk–benefit profile becomes less favorable to participants.

The lowest level of risk, often defined less than perspicuously as the risks of everyday life, applies to research with no realistic chance of harm and only minor discomfort, such as a blood draw. The guidelines agree that only minimal evidence is needed to enroll persons in this class of research. The next level covers research with the potential for moderate discomfort or harm but no realistic chance of serious morbidity or mortality. The guidelines generally agree that this class of research requires explicit evidence that enrollment is consistent with the person's remaining preferences and interests, as might be found in an advance directive.

A general statement authorizing research enrollment seems sufficient for performance of research-oriented positron emission tomography, but not for research that poses a realistic chance of serious harm. To mark this distinction, policies should include a third risk level for research that presents a realistic, although typically very low, chance of serious morbidity or mortality and no compensating potential for direct benefit. Enrollment in this class of research should be prohibited unless the available evidence convincingly shows that it is consistent with the person's remaining preferences and interests.

The New York, Maryland, NBAC, and Canadian Tri-Council guidelines try to implement the requirement for convincing evidence by limiting enrollment to persons who completed a research advance directive while competent. However, whether a formal advance directive provides convincing evidence of a person's re-

maining preferences and interests seems to depend on what it says and when it was executed. Moreover, it may be acceptable to enroll persons who, while competent, repeatedly and recently expressed a willingness to participate in a specific protocol but never formally recorded these wishes in an advance directive. Given these possibilities, a consensus policy could specify the amount of evidence required to enroll persons in each class of research but leave flexible the methods that may be used to provide it.

To help ensure that research enrollment decisions are based on patients' remaining preferences and interests, the six guidelines stipulate that persons who are unable to consent must have a proxy decision maker, usually a family member or close friend. The guidelines agree that proxies should make decisions based on what the patient would have decided if competent—the substituted judgment standard (16). Of course, in many cases, evidence of a person's competent preferences and interests as they relate to clinical research will be unclear or nonexistent. In such cases, decisions should be based on what is in the person's best interests.

The New York and Maryland guidelines specify that only proxies explicitly and formally appointed by patients may enroll them in research that does not offer a compensating potential for direct benefit. Whether this restriction adds additional protection is unclear. The literature from the clinical setting suggests that patient-appointed proxies often do not know patients' remaining preferences (17–20). Furthermore, specifying different classes of proxies adds a good deal of complexity. Thus, it may be clearer, and provide equal protection, to require that proxies make research decisions based on the substituted judgment and best interests standards. For persons who never selected a proxy while competent, a relationship hierarchy, such as those used by most states for clinical care, could be adopted to identify a research proxy.

The requirement that clinical investigators have sufficient evidence of patients' competent preferences and interests raises a question about the enrollment of adults who were never competent, such as those born with severe mental retardation. The six guidelines do not address this concern, presumably because there is no accepted analysis of how to protect such persons. Until an analysis is developed, it seems prudent to limit their enrollment to minimal risk research and research that offers the potential for direct benefit.

Assent and Dissent

There is near consensus among the guidelines that participants who express dissent should be withdrawn. The sole exception is the Canadian Tri-Council, which would allow research to continue if it offers the potential for direct benefit. However, dissenting participants should not be forced to take unproven treatments as part of research protocols that are designed to generate generalizable knowledge, not help the participants themselves. At the same time, dissenting participants need not be withdrawn automatically. Instead, research procedures could be stopped and further evaluation provided whenever a participant verbally objects or physically resists. Participants who express sustained dissent in any form should be withdrawn.

The proposals are divided over whether, in addition to the permission of a surrogate, clinical investigators should be required to obtain the agreement of impaired persons who are capable of providing it. Must patients with moderate Alzheimer disease who can understand that a protocol requires a 6-week hospital stay positively agree to enroll? The Maryland, New York, and Canadian Tri-Council guidelines endorse this "assent" requirement; the NBAC, NIH, and Council of Europe guidelines do not. The latter groups may assume that there is no reason to solicit the agreement of patients who are unable to consent. However, the abilities to understand and make decisions are continuous, not discrete. Many persons who are unable to consent can understand a good deal and can make decisions. Since persons with these abilities retain some autonomy, a consensus policy should stipulate that investigators must explain as much of the research plan as participants can understand and obtain the assent of those who are capable of providing it.

Independent Monitors

The six guidelines offer almost unanimous support for independent consent and participation monitors. The NIH and Canadian Tri-Council guidelines recommend them; the NBAC, New York, and Maryland guidelines require them for riskier research that does not offer the potential for direct benefit. The Council of

Table 3. **Required Safeguards in Specific Cases***

Study	Risk–Benefit Level	NIH	NBAC	Maryland	New York	Canadian Tri-Council	Council of Europe	Current Proposal
Blood draw	Minimal risk	No specific guidelines	Proxy consent, dissent, necessity, participant's condition	Proxy consent, assent–dissent, necessity, participant's condition	Proxy consent, assent–dissent, necessity, participant's condition	Proxy consent, dissent, necessity	Proxy consent, dissent, necessity, participant's condition	Proxy consent, assent–dissent, necessity, sufficient evidence
Two PET scans with arterial line	Minor increment over minimal risk—no potential benefit	Additional safeguards recommended	Proxy consent, dissent, necessity, participant's condition, explicit advance directive or approval of proxy, capacity monitor	Consent of participant's appointed proxy or documentation of wishes, assent–dissent, necessity, participant's condition, independent clinician	Proxy consent, assent–dissent, necessity, participant's condition	Proxy consent, dissent, necessity, advance directive	Not allowed	Proxy consent, assent–dissent, necessity, sufficient evidence
Drug withdrawal	Greater than a minor increment over minimal risk—no potential benefit	Additional safeguards recommended	Proxy consent, dissent, necessity, participant's condition, explicit advance directive or approval of proxy, capacity monitor	Consent of participant's appointed proxy, assent–dissent, necessity, participant's condition, advance directive, independent clinician, consent monitor	Consent of participant's appointed proxy, assent–dissent, necessity, participant's condition, advance directive, independent clinician, consent monitor	Proxy consent, dissent, necessity, advance directive	Not allowed	Proxy consent, assent–dissent, necessity, sufficient evidence, participation monitor, consent monitor
Phase II drug trial	More than minimal risk–potential for benefit	No additional safeguards required	Proxy consent, dissent, necessity, participant's condition, capacity monitor	Proxy consent, assent–dissent, participant's condition	Proxy consent, assent–dissent, participant's condition	Proxy consent, necessity	Proxy consent, dissent, necessity, participant's condition	Proxy consent, assent–dissent, necessity, sufficient evidence, participation monitor

* NBAC = National Bioethics Advisory Commission; NIH = National Institutes of Health; PET = positron emission tomography.

Europe guidelines do not mention independent monitors, presumably because the Council prohibits all research with greater than minimal risk that does not offer the potential for direct benefit.

Consent monitors are given a wide range of duties, including interpreting participants' advance directives (Maryland, New York) and acting as a witness to the consent process (NIH, Canadian Tri-Council). Perhaps their most important duty is to provide independent assurance that adults who have lost the ability to consent are enrolled in risky research only when sufficient evidence shows that it is consistent with their remaining preferences and interests.

Since the NBAC guidelines use only two risk levels, they endorse the use of a participation monitor for all research that carries greater than minimal risk and does not offer a potential for direct benefit. However, some research, such as positron emission tomography with arterial line, involves more than minimal risk but is unlikely to cause serious harm. In such cases, the patient's proxy and team members seem to offer adequate monitoring. By incorporating three risk levels, the Maryland, New York, and Canadian Tri-Council guidelines are able to limit the requirement for an independent participation monitor to research that presents a realistic chance of serious harm. The New York and Maryland guidelines do not require an independent participation monitor for research that offers the potential for direct benefit.

However, it is important to distinguish between safeguards that are needed whenever participants face serious risks and safeguards that are needed when par-

Table 4. **Roles and Responsibilities***

Variable	NIH	NBAC	Maryland	New York	Canadian Tri-Council	Council of Europe	Current Proposal
IRB	Review research; define risk–benefit; consider additional safeguards	Review research; define risk–benefit; require additional safeguards for riskier research	Review research; define risk–benefit; require additional safeguards for riskier research	Review research; define risk–benefit; require additional safeguards for riskier research	Review research; establish minimal acceptable risk; consider additional safeguards for riskier research	Review research	Review research; define risk–benefit; require additional safeguards for riskier research
Investigators	Explain study and enhance participants' understanding	Justify use of impaired participants; enhance autonomy; ensure well-being and continued willingness to participate	Justify use of impaired participants; ensure well-being and continued willingness to participate	Justify use of impaired participants; disclose IRBs that rejected the proposal; ensure well-being and continued willingness to participate	Justify use of impaired participants; ensure well-being and continued willingness to participate; establish minimal acceptable risk	Not mentioned	Enhance participants' consent; justify use of impaired participants; ensure well-being and continued willingness to participate
Institution	Not mentioned	Share responsibility	Not mentioned	Ensure IRB records are public	May assign person to report complaints	Not mentioned	Provide oversight and education to researchers; share responsibility
Government	Not mentioned	Define legally authorized proxy; sponsor studies on ethical issues	Study effects of regulations on participants and research	Provide oversight, guidance, and training for IRBs	Tri-Council has the right to review and audit research	Not mentioned	Provide IRB support; sponsor studies on ethical issues
Research team	Same as investigators	Not mentioned	Not mentioned	Act as participation monitors	Representatives explain information to participants and proxies	Not mentioned	Monitor participants' well-being, capacity to consent and continued willingness to participate
Family–proxies	Not mentioned	Participation monitors	Participation monitors	Participation monitors	Not mentioned	Not mentioned	Enrollment and participation monitors
Monitors	Not mentioned	Assess capacity; consider assessing consent	Monitor consent; monitor well-being in riskier research	Monitor consent; monitor well-being in riskier research	Provide information to participants and proxies	Not mentioned	Monitor consent for research that involves greater than a minor increment over minimal risk and is not clinically equivalent; monitor participation for risky research

* IRB = institutional review board; NBAC = National Bioethics Advisory Commission; NIH = National Institutes of Health.

ticipants face serious risks without a compensating potential for direct benefit. A compensating potential for direct benefit does not eliminate the risk for serious harm and therefore does not eliminate the need for a

participation monitor. In contrast, a compensating potential for direct benefit eliminates the assumption that enrollment is inconsistent with a patient's preferences and interests; therefore, it eliminates the need for an independent consent monitor.

Finally, some participants may lose the ability to consent after enrolling in protocols that were not reviewed for the participation of adults who are unable to consent. When this happens, the person's research participation should be placed on hold until the appropriate institutional review board can review it. When this review would result in an unacceptable delay, an independent monitor could assess whether continued research participation is consistent with the person's remaining preferences and interests and implement the appropriate additional safeguards in light of the protocol's risk–benefit profile.

In general, independent monitors should be well versed in the ethical requirements of informed consent and the concerns raised by conducting research with those who are unable to consent. Monetary support for independent monitors could be obtained as part of the grant application for research protocols.

APPLICATION OF THE PROPOSED SAFEGUARDS

To clarify the implications of the six proposed guidelines, **Table 3** illustrates their effect on several paradigm research protocols, for instance, research that poses a minor increment over minimal risk without the potential for direct benefit. An example might be two purely research-oriented positron emission tomography scans with arterial lines. The Council of Europe guidelines would prohibit this research. The other guidelines would allow it with additional safeguards. The Canadian Tri-Council requires an advance directive authorizing enrollment, Maryland requires that an independent clinician monitor patients' participation, the NBAC requires an independent consent monitor, and our proposed core safeguards would require explicit evidence that enrollment is consistent with patients' remaining preferences and interests. Finally, **Table 4** outlines the most prominent parties' responsibilities with respect to implementing the proposed safeguards.

CONCLUSION

In the absence of specific safeguards, research with adults who are unable to consent presents an increased potential for subject abuse. However, inappropriately stringent safeguards could halt important research and block improvements in medical care for the very groups the safeguards are designed to protect.

Four major groups in the United States have developed proposed additional safeguards, and two international guidelines already include such safeguards. These proposals agree on several safeguards, but disagree on others. By examining the proposed safeguards, and the arguments offered in support of them, we have identified six core safeguards that should be applied to all adults who are unable to consent to initial enrollment or continued research participation: 1) institutional review board risk–benefit assessment, 2) consent assessment, 3) necessity requirement, 4) proxy decision maker and sufficient evidence of participants' remaining preferences and interests, 5) respect for participant assent and dissent, and 6) independent monitors in some cases. By proactively adopting these safeguards before abuses occur, researchers can protect both adults who are unable to consent and the reputation of clinical research.

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We drove to Jonathan's parents' condominium in Jonathan's father's car, an enormous blue Oldsmobile. I had never seen Jonathan drive before. He looked both childlike and paternal behind the wheel of that big car. He held the wheel with both hands, as if he was steering a ship.

On the way he told us how his father's heart attack had struck him on his way to the mailbox. He explained that fact in particular. His father had had asthma and then emphysema. So his death by heart failure seemed to make everyone feel as cheated as they would have had he been in faultless health. Bobby asked, "On his way back from the *mail*box?" as if that were the most appalling thing about it.

I put on my sunglasses and watched the shopping centers pass. They shimmered in the heat.

Michael Cunningham
A Home at the End of the World
New York: Picador USA; 1990:221-2

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Submissions from readers are welcomed. If the quotation is published, the sender's name will be acknowledged. Please include a complete citation (along with page number on which the quotation was found), as done for any reference.–*The Editor*